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Cross-Intolerance With Bosutinib After Prior Tyrosine Kinase Inhibitors in Patients With Chronic Phase Chronic Myeloid Leukemia: BYOND Phase 4 Study

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Objective

- To evaluate the potential for cross-intolerance between bosutinib and prior TKIs in patients with CP Ph+ CML who were enrolled in the phase 4 BYOND study.

Conclusions

- Despite recurrence of certain same grade 1/2 or grade 3/4 AEs that caused prior TKI intolerance, these AEs were largely manageable with dose delays/reductions, with only 2 %, 7 %, and 0 % of imatinib-, dasatinib-, and nilotinib-intolerant patients, respectively, experiencing cross-intolerance with bosutinib.
- Patients who discontinued >1 prior TKI due to the same AE were rarely cross-intolerant to bosutinib.
- These findings support the use of bosutinib in patients with CP Ph+ CML intolerant to prior TKI treatment.

Plain Language Summary
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1. Devos T, et al. Acta Haematol 2019;142:197-207.
2. Bosulif® (bosutinib) prescribing information. Pfizer Inc; 2017.
3. Cortes JE, et al. Blood 2011;118:4567-76.
4. Cortes JE, et al. J Clin Oncol 2018;36:231-7.

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Background

- Some patients receiving a tyrosine kinase inhibitor (TKI) for chronic phase (CP) Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) may experience drug intolerance and require switching to an alternative TKI.
  - Approximately 40 % of patients with TKI treatment interruption/discontinuation due to intolerance reinitiate treatment with a different TKI.[1]
- Bosutinib, a TKI approved for newly diagnosed CP Ph+ CML and Ph+ CML resistant/intolerant to prior therapy,[2] has a distinct adverse event (AE) profile vs other TKIs used to treat Ph+ CML.[3,4]

Methods

- BYOND (NCT02228382) is an ongoing, phase 4, single-arm, open-label study of bosutinib (starting dose 500 mg once daily) in adult patients with CML resistant/intolerant to prior treatment.
- Cross-intolerance (permanent discontinuation of both prior TKI and bosutinib due to the same AE or AE cluster), recurrent AEs, and bosutinib dose modifications due to recurrent AEs were assessed across AEs and AE clusters.
- This analysis was based on ≥1 year after the last enrolled patient (median treatment duration 23.7 months [range, 0.2–42.2]; ~80 % with 2-year follow-up).
- For further details, please refer to the supplementary material that is downloadable using the QR code.

Results

- Of 141, 95, and 79 patients who received prior imatinib, dasatinib, or nilotinib, respectively, 63 (45 %), 70 (74 %), and 60 (76 %) were intolerant; patients were included in >1 group if they were intolerant to >1 prior TKI (**Table S1**).
- Median (range) treatment duration was 23.8 (0.4–41.9), 23.7 (0.2–42.2), and 23.6 (0.2–41.9) months in patients with imatinib intolerance, dasatinib intolerance, and nilotinib intolerance, respectively.
  - Median (range) dose intensity was 280.4 (79.7–500.0), 300.2 (125.0–500.0), and 305.8 (79.7–500.0) mg/day.
- No deaths occurred due to cross-intolerance between bosutinib and a prior TKI.
- A total of 15 patients discontinued >1 prior TKI due to the same AE; musculoskeletal pain and asthenia most frequently led to intolerance to >1 prior TKI (**Table S2**).
  - Only 1 patient with prior imatinib and dasatinib intolerance due to anemia was cross-intolerant to bosutinib.

IMATINIB-INTOLERANT PATIENTS

- No patient discontinued bosutinib due to AEs that most commonly caused imatinib intolerance (**Table 1**).
- Only 1 (2 %) imatinib-intolerant patient had cross-intolerance with bosutinib, which was due to anemia.

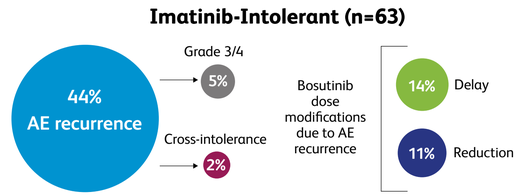

Table 1: Bosutinib Cross-Intolerance in Imatinib-Intolerant Patients

		Same AE With Bosutinib			Bosutinib Dose Modification Due to Same AE		Bosutinib Discontinued Due to Same AE‡
Cause of Intolerance*†, n (%)	n	Any Grade†	Grade 1/2†	Grade 3/4†	Delayed†	Reduced†	
Any AE	63	28 (44)	25 (40)	3 (5)	9 (14)	7 (11)	1 (2)
Musculoskeletal pain	19	10 (53)	9 (47)	1 (5)	1 (5)	2 (11)	0
Asthenia	10	6 (60)	6 (60)	0	1 (10)	1 (10)	0
Periorbital edema	9	1 (11)	1 (11)	0	0	0	0
Rash	7	1 (14)	1 (14)	0	0	0	0
Edema	6	3 (50)	3 (50)	0	0	0	0
Abdominal pain	3	2 (67)	2 (67)	0	1 (33)	1 (33)	0
Headache	3	2 (67)	2 (67)	0	0	0	0
Diarrhea	2	2 (100)	2 (100)	0	1(50)	0	0
Anemia	1	1 (100)	0	1 (100)	1 (100)	1 (100)	1 (100)
Neutropenia	1	1 (100)	0	1 (100)	1 (100)	1 (100)	0
Thrombocytopenia	1	1 (100)	0	1 (100)	1 (100)	0	0

* Includes AEs and AE clusters. † Causes present in ≥3 patients and AEs/AE clusters of interest are shown. ‡ Percentages based on patients having reported an AE on imatinib. AE=adverse event

DASATINIB-INTOLERANT PATIENTS

- The most common reason for prior dasatinib intolerance was pleural effusion (n=36); 14 patients had a recurrence and 1 discontinued bosutinib (**Table 2**).
  - Median (range) time to first event of pleural effusion with bosutinib was 233 (10–751) days.
- Other causes of cross-intolerance are shown in **Table 2**.

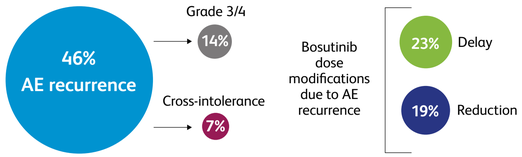

Table 2: Bosutinib Cross-Intolerance in Dasatinib-Intolerant Patients

		Same AE With Bosutinib			Bosutinib Dose Modification Due to Same AE		Bosutinib Discontinued Due to Same AE†
Cause of Intolerance*†, n (%)	n	Any Grade†	Grade 1/2†	Grade 3/4†	Delayed†	Reduced†	
Any AE	70	32 (46)	22 (31)	10 (14)	16 (23)	13 (19)	5 (7)
Pleural effusion	36	14 (39)	10 (28)	4 (11)	6 (17)	4 (11)	1 (3)
Dyspnea	8	4 (50)	4 (50)	0	3 (38)	3 (38)	1 (13)§
Headache	4	3 (75)	3 (75)	0	1 (25)	0	0
Rash	4	1 (25)	0	1 (25)	0	0	0
Musculoskeletal pain	3	2 (67)	2 (67)	0	0	0	0
Thrombocytopenia	3	1 (33)	0	1 (33)	1 (33)	1 (33)	0
Anemia	2	2 (100)	1 (50)	1 (50)	1 (50)	1 (50)	1 (50)
Nausea	2	1 (50)	1 (50)	0	1 (50)	0	1 (50)
Pulmonary hypertension	2	2 (100)	1 (50)	1 (50)	1 (50)	1 (50)	1 (50)
Diarrhea	1	1 (100)	0	1 (100)	1 (100)	1 (100)	0

* Includes AEs and AE clusters. † Causes present in ≥3 patients and AEs/AE clusters of interest are shown. ‡ Percentages based on patients having reported an AE on dasatinib. § Patient had both pleural effusion and dyspnea with dasatinib. While on bosutinib, patient had pericardial effusion, pleural thickening, and pulmonary lesion shortly before discontinuing due to dyspnea. AE=adverse event

NILOTINIB-INTOLERANT PATIENTS

- Few patients had recurrence of AEs that most commonly led to nilotinib intolerance (**Table 3**).
- No cross-intolerance with bosutinib was reported among nilotinib-intolerant patients.

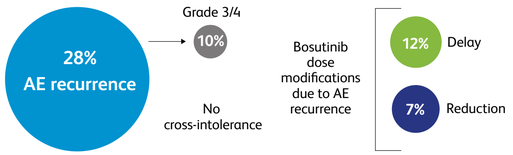

Table 3: Bosutinib Cross-Intolerance in Nilotinib-Intolerant Patients

		Same AE With Bosutinib			Bosutinib Dose Modification Due to Same AE		Bosutinib Discontinued Due to Same AE†
Cause of Intolerance*†, n (%)	n	Any Grade†	Grade 1/2†	Grade 3/4†	Delayed†	Reduced†	
Any AE	60	17 (28)	11 (18)	6 (10)	7 (12)	4 (7)	0
Musculoskeletal pain	6	1 (17)	1 (17)	0	0	0	0
Peripheral ischemia	6	1 (17)	0	1 (17)	0	0	0
Rash	6	0	0	0	0	0	0
Acute coronary syndrome	4	0	0	0	0	0	0
Asthenia	4	3 (75)	3 (75)	0	1 (25)	1 (25)	0
Diabetes mellitus	4	0	0	0	0	0	0
Hepatotoxicity	3	0	0	0	0	0	0
Pancreatitis	3	3 (100)	2 (67)	1 (33)	1 (33)	1 (33)	0
Diarrhea	2	2 (100)	2 (100)	0	1 (50)	0	0
Hematotoxicity	2	0	0	0	0	0	0
Leukopenia	1	0	0	0	0	0	0
Neutropenia	1	0	0	0	0	0	0
Pancytopenia	1	0	0	0	0	0	0
Thrombocytopenia	1	0	0	0	0	0	0

* Includes AEs and AE clusters. † Causes present in ≥3 patients and AEs/AE clusters of interest are shown. ‡ Percentages based on patients having reported an AE on nilotinib. AE=adverse event

Cross-Intolerance With Bosutinib After Prior Tyrosine Kinase Inhibitors in Patients With Chronic Phase Chronic Myeloid Leukemia: BYOND Phase 4 Study

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Methods

STUDY DESIGN

- In BYOND, patients with CP Ph+ CML (n=156) previously treated with imatinib, dasatinib, and/or nilotinib received bosutinib.
  - Dose reductions to 400, 300, and 200 mg once daily due to toxicity/tolerability were permitted.
  - Dosing interruptions were permitted for the management of treatment-related toxicity; the length of interruption was dependent on the severity and/or type of AE and time to recovery from AE, and dosing level upon treatment reintroduction was dependent on the severity and/or type of AE. Dose delays were defined as temporary dose interruptions due to toxicity.
- Intolerance to a prior TKI was defined as discontinuation due to an AE as the primary reason.
- Chest X-ray and an echocardiogram or multigated acquisition scan were performed at screening for each patient.

ADVERSE EVENT CLUSTERS

- AE clusters included prespecified Medical Dictionary for Regulatory Activities Terminology (v21.1) high-level terms (HLTs) and preferred terms (PTs) as indicated below.
  - Abdominal pain included PTs abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, and gastrointestinal pain.
  - Acute coronary syndrome included HLTs coronary necrosis and vascular insufficiency and ischemic coronary artery disorders and the PTs acute coronary syndrome, arteriosclerosis coronary artery, cardiovascular disorder, coronary angioplasty, coronary artery bypass, coronary arterial stent insertion, coronary artery bypass, coronary revascularization, coronary artery embolism, coronary artery thrombosis, coronary bypass thrombosis, coronary artery disease, coronary artery occlusion, coronary artery reocclusion, coronary artery restenosis, coronary artery stenosis, coronary artery thrombosis, coronary bypass stenosis, coronary bypass thrombosis, coronary vascular graft occlusion, and coronary vascular graft stenosis.
  - Anemia included PTs anemia and hemoglobin decreased.
  - Asthenia included PTs asthenia and fatigue.
  - Diabetes mellitus included HLTs diabetes mellitus (including subtypes) and hyperglycemic conditions not elsewhere classified and PTs blood glucose increased and glycosylated hemoglobin increased.
  - Edema included PTs generalized edema, edema, edema peripheral, fluid retention, and peripheral swelling.
  - Hepatotoxicity included PTs liver function test increased, transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, hepatic enzyme increased, hypertransaminasemia, hyperbilirubinemia, liver function test abnormal, alkaline phosphatase increased, hepatotoxicity, and blood bilirubin increased.
  - Leukopenia included PTs leukopenia and leukocyte decreased.
  - Musculoskeletal pain included PTs myalgia, arthralgia, muscle spasms, bone pain, musculoskeletal pain, and pain in extremity.
  - Neutropenia included PTs neutropenia and neutrophils decreased.
  - Pancreatitis included PTs pancreatitis acute, pancreatitis, lipase increased, hyperlipasemia, amylase increased, and hyperamylasemia.
  - Periorbital oedema included PTs eyelid edema, periorbital edema, and swelling of eyelid.
  - Peripheral ischemia included PTs peripheral artery thrombosis, peripheral arterial occlusive disease, peripheral arterial reocclusion, peripheral artery restenosis, peripheral artery stenosis, peripheral ischemia, peripheral artery angioplasty, peripheral artery bypass, peripheral artery stent insertion, peripheral revascularization, peripheral vascular disorder, ischemic limb pain, iliac artery disease, iliac artery occlusion, intermittent claudication, arterial bypass occlusion, arterial bypass thrombosis, femoral artery embolism, iliac artery embolism, peripheral artery thrombosis, peripheral embolism, spinal artery embolism, spinal artery thrombosis, subclavian artery embolism, subclavian artery thrombosis, subclavian artery occlusion, subclavian artery stenosis, subclavian artery embolus, subclavian stent thrombosis, and ankle brachial index decreased.
  - Rash included PTs rash, rash generalized, rash macular, rash maculopapular, rash papular, eczema, erythema, rash erythematous, exfoliative rash, drug eruption, and urticaria.
  - Thrombocytopenia included PTs platelet count decreased and thrombocytopenia.

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Results

Table S1: Demographics and Baseline Characteristics of Imatinib-, Dasatinib-, and Nilotinib-Intolerant Patients

n (%)*	Imatinib-Intolerant n=63	Dasatinib-Intolerant n=70	Nilotinib-Intolerant n=60
Age, median (range), y	61.0 (25.0–89.0)	64.5 (25.0–85.0)	60.0 (25.0–85.0)
Male	25 (39.7)	37 (52.9)	25 (41.7)
ECOG PS			
0	38 (60.3)	47 (67.1)	36 (60.0)
1	24 (38.1)	19 (27.1)	21 (35.0)
2	1 (1.6)	4 (5.7)	3 (5.0)
Number of prior TKIs			
1	22 (34.9)	3 (4.3)	4 (6.7)
2	26 (41.3)	31 (44.3)	18 (30.0)
3	15 (23.8)	36 (51.4)	38 (63.3)
Prior interferon	2 (3.2)	4 (5.7)	6 (10.0)
Prior imatinib	63 (100)	67 (95.7)	55 (91.7)
Prior dasatinib	30 (47.6)	70 (100)	39 (65.0)
Prior nilotinib	26 (41.3)	36 (51.4)	60 (100)

* Except where indicated.
ECOG PS=Eastern Cooperative Oncology Group performance status; TKI=tyrosine kinase inhibitor

Table S2: Causes of Intolerance to >1 Prior TKI

Cause of Intolerance*, n	Imatinib- and Dasatinib-Intolerant n=8	Imatinib- and Nilotinib-Intolerant n=9	Dasatinib- and Nilotinib-Intolerant n=6	Imatinib-, Dasatinib-, and Nilotinib-Intolerant n=4
Musculoskeletal pain	2	2	0	0
Asthenia	1	3	1	1
Depression	1	1	1	1
Headache	1	1	1	1
Pain	1	1	1	1
Alveolitis	1	0	0	0
Anemia	1†	0	0	0
Periorbital edema	1	0	0	0
Hematotoxicity	0	1	0	0
Hypersomnia	0	1	0	0
Conjunctivitis	0	0	1	0
Diabetes mellitus	0	0	1	0
Pleural effusion	0	0	1	0
Rash	0	0	1	0

* Includes AEs and AE clusters.
† Patient was cross-intolerant to bosutinib.
TKI=tyrosine kinase inhibitor

- Of 63 imatinib-intolerant patients, 32 (51 %) discontinued bosutinib (21 [33 %] due to AEs; **Table S3**), but only 1 (2 %) had cross-intolerance.
- Of 70 dasatinib-intolerant patients, 33 (47 %) discontinued bosutinib (20 [29 %] due to AEs; **Table S3**); 5 (7 %) had cross-intolerance.
- Of 60 nilotinib-intolerant patients, 26 (43 %) discontinued bosutinib (13 [22 %] due to AEs; **Table S3**), 0 due to cross-intolerance.

Table S3: Reasons for Treatment Discontinuation in Imatinib-, Dasatinib-, and Nilotinib-Intolerant Patients

n (%)*	Imatinib-Intolerant n=63	Dasatinib-Intolerant n=70	Nilotinib-Intolerant n=60
Total treatment discontinuations	32 (51)	33 (47)	26 (43)
AE	21 (33)	20 (29)	13 (22)
Related to study treatment	14 (22)	17 (24)	11 (18)
Unrelated to study treatment	7 (11)	3 (4)	2 (3)
Patient died	1 (2)	0	1 (2)
Insufficient clinical response	1 (2)	2 (3)	2 (3)
Noncompliance with study treatment	4 (6)	1 (1)	3 (5)
Investigator declined further study participation	0	1 (1)	1 (2)
Protocol violation	1 (2)	2 (3)	2 (3)
Lost to follow-up	0	0	1 (2)
Patient refused continued treatment for reason other than AE	3 (5)	4 (6)	2 (3)
Other	1 (2)	3 (4)	1 (2)

AE=adverse event